

Treating Chemotherapy Induced Peripheral Neuropathy with Physical Therapy: A Case Series

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Abstract

Purpose: Chemotherapy-induced peripheral neuropathy (CIPN) can be seen in 19-85% of the patients treated with neurotoxic chemotherapy. Although pharmacotherapy has been shown to be better than placebo, its efficacy remains modest. Currently there are no clinical practice guidelines for the treatment of CIPN with physical therapy (PT).

Case Description: This case series follows 2 patients with a history of multiple myeloma and bone marrow transplant, through 10 and 13 weeks of skilled PT for treatment of CIPN. Patients were treated 1x per week in clinic with manual therapy including soft tissue massage, trigger point release, joint mobilization to the feet, a therapeutic exercise program including an ankle resistance exercise and standing stretches, neuromuscular re-education addressed with balance training, and were given a daily home exercise program.

Results: Improved scores on the Neuropathic Pain Diagnostic Questionnaire (5/10 with 41 for interference reduced to 3/10 with 12 for interference and 5/10 with 29 for interference reduced to 1/10 with 4 for interference), reduced fall risk on the 4-Stage Balance Test, and decreased VAS pain ratings (10/10 reduced to 0/10 during the day and 4/10 at night and 8/10 reduced to 0/10 all times).

Conclusion: This case series shows positive effect for patients with multiple myeloma treated for CIPN with PT 1x per week in clinic combined with a home program. Future studies should consider combined therapies for treatment as well as more precise outcome measures and functional tests.

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is currently classified as damage to the peripheral nerves caused by exposure to a neurotoxic chemotherapeutic agent. [1,2] Damage done to DNA structure, nerve axons, dorsal root ganglia, mitochondria, glial cells, sodium, calcium and potassium ion channels may be the pathophysiologic mechanism underlying CIPN leading to neuroinflammation and altered excitability of peripheral neurons. [1,3,4] According to published literature, the incidence of CIPN is about 19-85% for patients treated with neurotoxic chemotherapy at 6 months post chemotherapy and it can affect subjects of all age groups. [1,4,5] Sensory signs and symptoms may include numbness, tingling, burning, pain, ataxia, loss of deep tendon reflexes, and reduced sense of touch, vibration and proprioception. [1,3] Motor symptoms include weakness, balance disturbances, difficulty performing fine motor skills, diminished or absent deep tendon reflexes, slower gait speed, and increased frequency of falls, accompanied by significant limitations in activities of daily living. [1,3,5,6]

Medications for the treatment of CIPN, such as commonly prescribed gabapentin, are not always effective despite benefits illustrated from rat models. [4] A recent randomized controlled trial showed that only duloxetine showed some benefit for reduction of CIPN symptoms. [4] Lack of effectiveness of

medication leads clinicians and patients to look for other models of care for this common side effect. Scrambler therapy, acupuncture, and physical therapy have been studied for their benefit to this patient population.

The evidence is beginning to show that physical therapy can be effective to reduce the effects of CIPN and help patients decrease pain, increase balance, increase endurance and increase quality of life. A systematic review from 2018 looked at 5 studies covering different physical therapy interventions such as walking programs, cycling programs, strength training with resistance bands, core stabilizations, sensorimotor training and work on balance. [5] The conclusion reported that significant changes can be made when treatment includes aerobic exercise, strength and proprioceptive training with a frequency of 2-5x per week. The EXCAP (exercise for cancer patients) multi-center randomized controlled trial from 2018 evaluated patients, mainly with breast cancer, with CIPN, related to taxane, platinum, or vinca alkaloid-based chemotherapy, and supported a home based walking and resistance exercise program as effective in decreasing numbness and tingling in the hands and the feet. [7] When considering the safety of exercise for patients with cancer, physical therapy at moderate and high intensity can be safe as seen in the 2015 PACES randomized clinical trial looking at effectiveness of supervised activity programs for patients undergoing treatment for breast cancer. [8] A 2020 comprehensive review looked at 13 studies for exercise effects on CIPN and while they found balance training and aerobic exercise, prescribed on average for 8-12 weeks, effective, reviewers noted the guidelines continue to be too heterogeneous. [9] Our case review offers to show that a combination of treatments, with specific guidelines, is easy to follow and can be successful for the treatment of CIPN in patients with multiple myeloma after 8-12 weeks of 1x per week clinic sessions combined with a daily home exercise program.

Case Description

This case series examines the combination of manual therapy, therapeutic exercise, and neuromuscular re-education, as suggested to be effective per the literature reflected on above, for the successful physical therapy treatment for patients with CIPN. This case series was prepared following the CARE guidelines. [10] This case series took place during 2020-2021, during the COVID-19 pandemic, and all safety measures such as masks, hand washing, and sanitizing the rooms and equipment between patient use were strictly adhered to.

Over the course of 10-13 weeks, the following 2 patients were seen for skilled physical therapy at Hollings Cancer Center. The 2 male patients, ages 73 and 61, were both diagnosed with multiple myeloma, and had received proteasome inhibitor-based therapy. Neither patient had a known history of diabetes mellitus, alcohol use, or nutritional / vitamin deficiencies, and neither reported neuropathy prior to initiation of treatment for cancer. Each patient was seen once per week, unless the patient had conflicting appointments or family obligations. Frequency was chosen to support hands on treatment and

education, balanced with keeping patients socially distanced and not wanting them to have to come into clinic more than necessary during the COVID-19 pandemic.

When first seen in clinic, both patients reported feeling like they were walking on rocks/sand, not being able to walk as far as they previously could, and experienced worsening pain at night with difficulty going to sleep. Patient A rated the pain at 10/10 on average and Patient B rated the pain as 8/10 on average at the initial evaluation. VAS pain scale was chosen based on NCCN Guidelines Version 1.2020 Adult Cancer Pain. [11]

During initial visit, each patient was evaluated for overall range of motion (ROM), muscle strength and gait disturbances as defined for examination and evaluation from the APTA Guide to Physical Therapist Practice and taught in the following textbooks: Daniel and Worthington's Muscle Testing, Measurement of Joint Motion: A Guide to Goniometry and Muscle Testing and Function. [12,13,14,15] Feet were examined for sensations of light versus deep touch, joint mobility and tenderness to palpation. Current level of function and dysfunction were recorded based on the International Classification of Functioning, Disability and Health (ICF) model. [16]

For self-reported disability each patient filled out the Neuropathic Pain Diagnostic Questionnaire (DN4). [17] The DN4 assesses 7 patient-rated questions for symptoms: burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching. A patient score of >4/10 indicates the presence of neuropathy. The second page of the DN4 asks about interference in general activity, mood, normal work, relationships, sleep, and enjoyment of life on a 0-10 scale with 10 being completely interferes with their quality of life. Patient A rated their symptoms as 5/10 with a 41 for interference on quality of life. Patient B rated their symptoms as 5/10 with a 29 for interference for quality of life.

For balance assessment each patient was taken through the 4-Stage Balance Test. The 4-Stage Balance Test is a recommended measure from the Centers for Disease Control and Prevention STEADI (Stopping Elderly Accidents, Deaths, and Injuries) falls campaign to recognize fall risk. An adult who cannot hold tandem stance for 10 seconds is at a higher risk for falls. [18] Patient A was able to stand in tandem stance for 2 seconds on each side. Patient B was able to stand on single leg stance for 10 seconds on each side.

Therapeutic Intervention

The protocol followed for the treatment of patients with CIPN at Hollings Cancer Center was developed to combine manual therapy, strength and stretching, and balance activity. This was developed based on clinical practice as standard of care for patients with CIPN and did not require a review or approval from an IRB. The goal was to address the sensory and motor symptoms that come with CIPN, affecting pain, strength and fall risk for this patient population.

A 2016 systematic review on diabetic peripheral neuropathy (DPN) found that reflexology of the feet compared with pharmacological treatment, and Thai foot massage compared with health education, had significant positive effects on decreasing DPN symptoms. [19] A 2015 study on the effects of Thai foot massage on balance found that using direct deep pressure combined with gentle distraction on the muscles and joints of the foot and lower leg increased local blood circulation and stimulated the somatosensory system. [20] The parallel randomized controlled trial posited that these effects may reverse neuropathy by changing pressure distribution, proprioceptive systems, muscle tension, joint angle and muscle length. [20]

The “neuropathy massage” technique performed on and taught to patients in this study is derived from the above literature. Patients begin by massaging the heel, then work with pressure applied by the thumbs up through the arch of the foot, working to the ball of the foot. Patients then move to the top of the foot, working to apply soft and then deeper pressure in between the metatarsals, looking for and releasing trigger points in the muscles. When trigger points are found, patients are instructed to hold each trigger point for 30 to 90 seconds to get the muscles to relax. Joint mobilization is then performed on all metatarsals with grade III mobilization, looking for fluid movement between the bones. Pain free distraction is then performed on all the toes. The technique is finished with sweeping glides through the top of the foot to push any edema in the direction of lymphatic flow and the patient finishes with 5 ankle circles in each direction.

With CIPN, motor symptoms include weakness. Physiologically muscle activation happens in relation to action potentials triggered by voltage-gated ion channels. [21] Resistance training has been shown to increase muscle activation at the motor and neural level from the resting potential of the ion channel, to the number of muscle fibers recruited, up the nerve pathway and to the brain for motor plasticity and control. [22,23] The ankle 4-way is a progressive resistance exercise working on ankle dorsiflexion, plantarflexion, inversion and eversion with a Thera-Band. The ankle 4-way exercise was performed with a yellow Thera-Band (3 pounds of resistance) 10 times in each direction, on each foot, for homework daily. Patients worked their way up to 30 repetitions in each direction and then resistance was increased to a red (3.7 pounds of resistance) Thera-Band and then a green (4.6 pounds of resistance) Thera-Band when good eccentric control for 30 repetitions per foot in the directions of dorsiflexion, plantarflexion, inversion,

and eversion were achieved. [24] The exercise was followed with the gastrocnemius, soleus, and plantar fascia stretches, which were held for one minute in each position on each leg.

The annual fall rate for adults 65 years and older is about 30%. Studies have shown that more than 50% of cancer survivors have fallen at least once within the preceding 12-month period. [2] Loss of balance contributed to more than 50% of falls among cancer survivors receiving neurotoxic chemotherapy. [4] As a 2019 study from BMC Cancer shows, balance training can promote neuronal adaptation, improving muscle output and postural control. [25] Patients worked on standing in semi-tandem, tandem and single leg stance, with eyes open, eyes closed, and on solid and uneven surfaces to increase balance.

On initial evaluation both Patient A and Patient B received manual therapy following the neuropathy massage technique, were instructed on how to perform it on themselves, were instructed to have family members assist in performing it and were given handouts with the directions. Patients were instructed to rub their feet for at least five minutes, per foot, per day. On follow up, patients were treated with the neuropathy manual therapy technique from the licensed physical therapist, and performed the ankle 4-way exercise, standing gastrocnemius stretch, standing soleus stretch and standing plantar fascia stretches. In later sessions, patients worked on balance training on solid ground and on a blue foam instability pad, with eyes open, with eyes closed, with head turns, and with dual tasking brain games. In the final few weeks of treatment, an exercise to isolate the toes and work on lifting up one toe at a time was added for increased proprioception and muscle control through the foot.

Outcomes

Patient A was seen for 10 visits over the course of 13 weeks. Patient B was seen for 8 visits over the course of 10 weeks. At evaluation and at discharge both patients had ROM within normal limits for the ankle and manual muscle testing rated strength within functional limits. On discharge, Patient A reported a DN4 score of 3/10 with 12 for interference in quality of life and pain rating of 0/10 with 4/10 pain in the feet only on some nights. Patient B reported a DN4 score of 1/10 with 4 for interference in quality of life and a pain rating of 0/10. On discharge, reduction in fall risk as seen with the 4-Stage Balance Test showed that Patient A was able to stand in tandem stance and single leg stance for 10 seconds on each foot on solid ground with eyes open, and Patient B was able to stand in tandem stance for >10 seconds and single leg stance for 1 minute on solid ground with eyes open. Both patients reported that they were following the neuropathy massage directions 3 times daily, were performing the stretches 1 time daily, and were performing the ankle 4-way and toe isolation exercises 3-4 times per week. Both patients were discharged as they had mastered the neuropathy massage technique, were independent with their own home exercise and walking programs, achieved balance scores to indicate a decreased risk for falling, and reported improved quality of life and had the tools to continue to get stronger with decreased CIPN outside of skilled physical therapy.

See attached tables for clinical presentations, interventions, and outcomes of the 2 patients with CIPN.

Discussion

Chemotherapy induced peripheral neuropathy can result in increased risk for falls, pain, numbness, difficulty sleeping, compromised compliance with cancer treatment, and decreased quality of life. Current literature reviews that walking programs, cycling programs, strength training with resistance bands, core stabilizations, sensorimotor training and work on balance are effective for the treatment of CIPN, particularly when combined. [5,6,7,8,9] Exercise has been shown to be helpful in supervised and home-based programs, and safe at the moderate to high intensity level. [8] The American College of Sports Medicine Guidelines for Exercise and Cancer has guidelines for cancer-related fatigue, health-related QOL, physical function, anxiety, depression and lymphedema with strong evidence and moderate evidence for bone health and sleep, but lacks recommendations for CIPN. [26] According to the 2020 Recommendations for Prevention and Management of Chemotherapy-Induced Peripheral Neuropathy from the American Society of Clinical Oncology though they are eager to identify a treatment for CIPN, there is insufficient data to recommend treatments such as exercise. [27]

Over the course of <15 weeks, with manual therapy, combined with strength, stretching, and balance training as a protocol developed from literature review and clinical practice, these 2 patients were able to experience clinically significant differences in pain on the VAS scale, improvement in symptoms on their DN4 scores, decreased risk for falls as seen with the 4-Stage Balance Test and improvement in quality of life when looking at self-report and interference ratings on the DN4. Our protocol, as laid out in table 2, combines manual therapy, resistance training and balance training as the literature suggests, is a combination of in clinic and at home work, and per patient report is easy to follow. With improvements in cancer treatments and survival outcomes, there needs to be more evidence-based recommendations on how to help patients with CIPN so that they can tolerate treatment and continue to work towards a better quality of life. This study aims to contribute to the work towards specific clinical practice guideline for treating patients with CIPN.

Limitations to this case series are the small number of patients. Future studies with more patients and possible randomized controlled trials are needed and are in the initial stages of development at the Hollings Cancer Center at the Medical University of South Carolina. There are limitations to the DN4 as it has not been validated for CIPN and an alternate would be to use the Functional Assessment of Cancer Therapy, Gynecologic Oncology Group-Neurotoxicity Scale (FACT/GOG-NTX) as per the Academy of Oncologic Physical Therapy EDGE Task Force Report Summaries from 2019. [28] Additionally, as a 2017 article in Nursing points out, many neuropathy ratings are based on patient perspective and while the

FACT/GOG-NTX or the Modified Total Neuropathy Score (mTENS) are helpful, other objective measures need to be present. [29] Functional tests such as monofilament testing, the 5x sit to stand test and dynamometer strength testing as noted in the EDGE task force summaries should be considered. [28]

Declarations

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Conflicts of Interest: The authors declare that there are no conflicts of interest to disclose.

Availability of Data and Material: All data can be made available, and all HIPAA guidelines will be followed for any requested data.

Code Availability: Not Applicable.

Author's Contributions: All authors contributed to the manuscript design. Material preparation, data collection, and analysis was performed by Dr. Katie Schmitt. The drafts of the manuscript were collaborated on by Dr. Katie Schmitt, Dr. David Cachia and Dr. Hamza Hashmi. All authors read and approve the final manuscript.

Ethics Approval: This is an observational case series and therefore no IRB presentation or ethics review from the Medical University of South Carolina is required.

Consent to Participate: Both Patient A and Patient B have agreed to be a part of this case series and agree to have the report be submitted for publication. Both patients have had the opportunity to review the study and have filed patient consent forms.

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Tables

Table 1

Pt	Age	Cancer Type	# of visits	# weeks	Data Obtained	DN4	4 stage balance scores	Pain
A	73	MM	10	13	Initial Eval	5/10 c 41 interference	tandem 2 seconds B	10/10.
					Progress Report 1	4/10 c 8 interference	tandem 10 seconds B SLS 5 seconds B	
					Progress Report 2	4/10 c 17 interference	tandem 10 seconds SLS R:12 seconds, L:5 sec.	
					Discharge	3/10 c 12 interference	tandem 10 seconds B SLS: 10 seconds B	0/10 c 4/10 night
B	61	MM	8	10	Initial Eval	5/10 c 29 interference	SLS 10 seconds B	8/10.
					Progress Report	1/10 c 6 interference	SLS 30 seconds B	
					Discharge	1/10 c 4 interference	SLS 1 minute B	0/10.

Table 2

Physical Therapy Protocol for Treatment of CIPN

- Week 1: Initial evaluation and initiation of neuropathy massage
- Week 2: Neuropathy massage and initiation of ankle 4-way with yellow Thera-band
- Week 3: Review massage and ankle 4-way with addition of gastrocnemius, soleus and fascia stretches
- Week 4: Neuropathy massage, ankle 4 way, stretches, begin balance training progressing from feet together to semi-tandem, tandem and then single leg stance
- Week 5-12: Neuropathy massage. Progress ankle 4-way with increased resistance when 30 repetitions in dorsiflexion, plantarflexion, inversion and eversion show good eccentric control. Progress balance training for eyes open, eyes closed, with decreased base of support, on even and uneven ground. Work on home exercise program which includes walking program.

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